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(54) Title: NONINVASIVE DETERMINATION OF CARDIAC OUTPUT, PULMONARY BLOOD FLOW, AND BLOOD GAS CONTENT
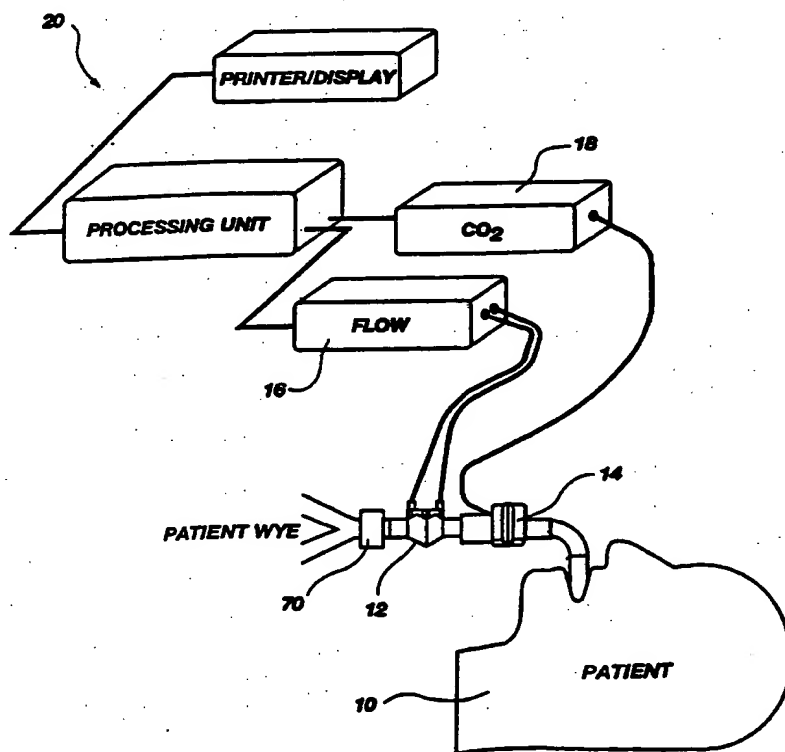
(57) Abstract: A method of noninvasively determining the pulmonary capillary blood flow or cardiac output of a patient, including the use of rebreathing techniques to measure the respiratory flow and carbon dioxide pressure of the patient's breathing. These measurements are used to calculate carbon dioxide elimination and an indicator of the carbon dioxide content of the patient's blood, such as the end tidal pressure of carbon dioxide ($PetCO_2$), $CaCO_2$, or pCO_2. The location and orientation of a best-fit line through the carbon dioxide elimination data and the data of the indicator of carbon dioxide content is determined by linear regression or by plotting the carbon dioxide elimination data against the data of the indicator of carbon dioxide content. At least one set of the data is modified and at least one other determination of the best-fit line made to find a data set that correlates most closely to the best fit line. The data may be modified by filtering or clustering. The slope of the best-fit line that correlates most closely to the data is then used to determine the pulmonary capillary blood flow or cardiac output of the patient. When the indicator of carbon dioxide content is $CaCO_2$, the negative of the slope of the best fit line is equal to the pulmonary capillary blood flow of the patient.

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NONINVASIVE DETERMINATION OF CARDIAC OUTPUT, PULMONARY BLOOD FLOW, AND BLOOD GAS CONTENT

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TECHNICAL FIELD

The present invention relates to methods and apparatus for accurately, noninvasively measuring the pulmonary capillary blood flow, cardiac output, and mixed venous carbon dioxide content of the blood of a patient. Particularly, the present invention relates to a method and apparatus for noninvasively measuring pulmonary capillary blood flow or cardiac output that employs an algorithm to increase the accuracy of data upon which the pulmonary capillary blood flow or cardiac output measurement is based.

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BACKGROUND

Carbon dioxide elimination (V_{CO_2}) is the volume of carbon dioxide (CO_2) excreted from the body of a patient during respiration. Conventionally, carbon dioxide elimination has been employed as an indicator of metabolic activity. Carbon dioxide elimination has also been used in re-breathing methods of determining pulmonary capillary blood flow and cardiac output.

The carbon dioxide Fick equation:

$$Q = V_{CO_2}/(CvCO_2 - CaCO_2),\qquad\qquad(1)$$

where Q is cardiac output, $CvCO_2$ is carbon dioxide content of the venous blood of the patient, and $CaCO_2$ is the carbon dioxide content of the arterial blood of the patient, has been employed to non-invasively determine the pulmonary capillary blood flow or cardiac output of a patient. The carbon dioxide elimination of the patient may be non-invasively measured as the difference per breath between the volume of carbon dioxide inhaled during inspiration and the volume of carbon dioxide exhaled during expiration, and is typically calculated as the integral of the carbon dioxide signal, or the fraction of respiratory gases that comprises carbon dioxide, or "carbon dioxide fraction," times the rate of flow over an entire breath.

The partial pressure of end tidal carbon dioxide ($PetCO_2$ or $etCO_2$) is also measured in rebreathing processes. The partial pressure of end-tidal carbon dioxide,

after correcting for any deadspace, is typically assumed to be approximately equal to the partial pressure of carbon dioxide in the alveoli ($PACO_2$) of the patient or, if there is no intrapulmonary shunt, the partial pressure of carbon dioxide in the arterial blood of the patient ($PaCO_2$).

5　　　　Rebreathing is typically employed either to non-invasively estimate the carbon dioxide content of mixed venous blood (as in total rebreathing) or to obviate the need to know the carbon dioxide content of the mixed venous blood (by partial rebreathing). Rebreathing processes typically include the inhalation of a gas mixture that includes carbon dioxide. During rebreathing, the carbon dioxide elimination of the patient

10　decreases to a level less than during normal breathing. Rebreathing during which the carbon dioxide elimination decreases to near zero is typically referred to as total rebreathing. Rebreathing that causes some decrease, but not a total cessation of carbon dioxide elimination, is typically referred to as partial rebreathing.

　　　　Rebreathing is typically conducted with a rebreathing circuit, which causes a

15　patient to inhale a gas mixture that includes carbon dioxide. FIG. 1 schematically illustrates an exemplary rebreathing circuit 50 that includes a tubular airway 52 that communicates air flow to and from the lungs of a patient. Tubular airway 52 may be placed in communication with the trachea of the patient by known intubation processes, or by connection to a breathing mask positioned over the nose and/or mouth of the

20　patient. A flow meter 72, which is typically referred to as a pneumotachometer, and a carbon dioxide sensor 74, which is typically referred to as a capnometer, are disposed between tubular airway 52 and a length of hose 60, and are exposed to any air that flows through rebreathing circuit 50. Both ends of another length of hose, which is referred to as deadspace 70, communicate with hose 60. The two ends of deadspace 70

25　are separated from one another by a two-way valve 68, which may be positioned to direct the flow of air through deadspace 70. Deadspace 70 may also include an expandable section 62. A Y-piece 58, disposed on hose 60 opposite flow meter 72 and carbon dioxide sensor 74, facilitates the connection of an inspiratory hose 54 and an expiratory hose 56 to rebreathing circuit 50 and the flow communication of the

30　inspiratory hose 54 and expiratory hose 56 with hose 60. During inhalation, gas flows into inspiratory hose 54 from the atmosphere or a ventilator (not shown). During normal breathing, valve 68 is positioned to prevent inhaled and exhaled air from

flowing through deadspace 70. During rebreathing, valve 68 is positioned to direct the flow of exhaled and inhaled gases through deadspace 70.

The re-breathed air, which is inhaled from deadspace 70 during rebreathing, includes air that has been exhaled by the patient (i.e., carbon dioxide-rich air).

During total rebreathing, substantially all of the gas inhaled by the patient was expired during the previous breath. Thus, during total rebreathing, the partial pressure of end-tidal carbon dioxide ($PetCO_2$ or $etCO_2$) is typically assumed to be equal to or closely related to the partial pressure of carbon dioxide in the arterial ($PaCO_2$), venous ($PvCO_2$), or alveolar ($PACO_2$) blood of the patient. Total rebreathing processes are based on the assumption that neither pulmonary capillary blood flow nor the content of carbon dioxide in the venous blood of the patient ($CvCO_2$), changes substantially during the rebreathing process. The partial pressure of carbon dioxide in blood may be converted to the content of carbon dioxide in blood by means of a carbon dioxide dissociation curve, where the change in the carbon dioxide content of the blood ($CvCO_2$ - $CaCO_2$) is equal to the slope (s) of the carbon dioxide dissociation curve multiplied by the measured change in end tidal carbon dioxide ($PetCO_2$) as effected by a change in effective ventilation, such as rebreathing.

In partial rebreathing, the patient inhales a mixture of "fresh" gases and gases exhaled during the previous breath. Thus, the patient does not inhale a volume of carbon dioxide as large as the volume of carbon dioxide that would be inhaled during a total rebreathing process. Conventional partial rebreathing processes typically employ a differential form of the carbon dioxide Fick equation to determine the pulmonary capillary blood flow or cardiac output of the patient, which do not require knowledge of the carbon dioxide content of the mixed venous blood. This differential form of the carbon dioxide Fick equation considers measurements of carbon dioxide elimination, $CvCO_2$, and the content of carbon dioxide in the alveolar blood of the patient ($CACO_2$) during both normal breathing and the rebreathing process as follows:

$$Q_{pcbfBD} = \frac{VCO_{2B} - VCO_{2D}}{(CvCO_{2B} - CvCO_{2D}) - (CACO_{2B} - CACO_{2D})}, \tag{2}$$

where VCO_{2B} and VCO_{2D} are the carbon dioxide production of the patient during before rebreathing and during the rebreathing process, respectively, and $CvCO_{2B}$ and $CvCO_{2D}$ are the content of CO_2 of the venous blood of the patient before rebreathing and during

the rebreathing process, respectively. In using the differential Fick equation to calculate cardiac output, C_ACO_{2B} and C_ACO_{2D}, the contents of CO_2 in the arterial blood of the patient before rebreathing and during rebreathing, respectively, are substituted in equation (2) for the C_ACO_2 measurements.

5 Again, with a carbon dioxide dissociation curve, the measured $PetCO_2$ can be used to determine the change in content of carbon dioxide in the blood before and during the rebreathing process. Accordingly, the following equation can be used to determine pulmonary capillary blood flow or cardiac output when partial rebreathing is conducted:

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$$Q = \Delta VCO_2/s\Delta PetCO_2. \qquad\qquad (3)$$

Alternative differential Fick methods of measuring pulmonary capillary blood flow or cardiac output have also been employed. Such differential Fick methods typically include a brief change of $PetCO_2$ and VCO_2 in response to a change in effective ventilation. This brief change can be accomplished by adjusting the respiratory rate,

15 inspiratory and/or expiratory times, or tidal volume. A brief change in effective ventilation may also be effected by adding CO_2, either directly or by rebreathing. An exemplary differential Fick method that has been employed, which is disclosed in Gedeon, A. et al. in 18 *Med. & Biol. Eng. & Comput.* 411-418 (1980), employs a period of increased ventilation followed immediately by a period of decreased ventilation.

20 The carbon dioxide elimination of a patient is typically measured over the course of a breath by the following, or an equivalent, equation:

$$VCO_2 = \int_{breath} V \times f_{CO2}\, dt, \qquad\qquad (4)$$

where V is the measured respiratory flow and f_{CO2} is the substantially simultaneously detected carbon dioxide signal, or fraction of the respiratory gases that comprises

25 carbon dioxide or "carbon dioxide fraction."

Due to the measured respiratory constituents upon which VCO_2 and $PetCO_2$ calculations are made, VCO_2 typically responds to rebreathing about one breath before $PetCO_2$ for the same breath. Accordingly, a VCO_2 signal may lead a $PetCO_2$ signal by about one breath. Thus, at a particular point in time, the VCO_2 and $PetCO_2$ signals do

30 not correspond to one another. As these values are often used to noninvasively determine pulmonary capillary blood flow or cardiac output, the lack of correspondence

between these values may lead to inaccuracies in the pulmonary capillary blood flow or cardiac output determination.

In addition, measurements that are taken during spurious breaths, or breaths which do not provide information relevant to pulmonary capillary blood flow or cardiac output, may act as noise that introduces inaccuracy into the noninvasive pulmonary capillary blood flow or cardiac output determination.

When equation (4) is employed to calculate the carbon dioxide elimination of the patient from the respiratory flow and carbon dioxide fraction measurements over an entire breath, such miscorrelation or noise-induced inaccuracies in either the expiratory flow, the inspiratory flow, or both may cause inaccuracies in the carbon dioxide elimination determination or inconsistencies between carbon dioxide elimination determinations.

Accordingly, there is a need for a method of accurately, noninvasively calculating pulmonary capillary blood flow and cardiac output.

DISCLOSURE OF INVENTION

The present invention includes a method and apparatus for noninvasively measuring pulmonary capillary blood flow and cardiac output. The present invention includes the use of known rebreathing techniques to substantially noninvasively obtain carbon dioxide elimination (VCO_2) and partial pressure of end tidal carbon dioxide ($PetCO_2$) measurements of a patient's breathing. These measurements may then be used to calculate pulmonary capillary blood flow or cardiac output of the patient by employing the following equation:

$$Q = \frac{\Delta VCO_2}{\Delta CaCO_2} = \frac{\Delta VCO_2}{s\Delta PetCO_2} \tag{5}$$

where s is the slope of a standard carbon dioxide (CO_2) dissociation curve, ΔVCO_2 is the change in the carbon dioxide elimination of the patient due to a change in effective ventilation, such as that caused by rebreathing, and $\Delta CaCO_2$ and $\Delta PetCO_2$ are the change in the content of carbon dioxide in the arterial blood of the patient and the change in the end tidal partial pressure of carbon dioxide of the patient, respectively, due to the same change in effective ventilation. Alternatively, a standard carbon

dioxide dissociation curve can be used to determine $\Delta CaCO_2$ on the basis of the measured $\Delta PetCO_2$.

As an alternative to the use of the above equations to determine pulmonary capillary blood flow or cardiac output, the substantially noninvasive VCO_2 and $CaCO_2$

5   measurements can be related to each other in a linear fashion. This can be visually diagramed by plotting the VCO_2 and $CaCO_2$ measurements against one another on a two-dimensional (X-Y) line graph. The negative slope ($-1 \times m$) of the best-fit line through the data is approximately equal to the pulmonary capillary blood flow. The appropriate location and orientation of such a best-fit line may be calculated by linear

10   regression or least squares. Depending on the correlation between the calculated best-fit line and the measured data, it may also be desirable to modify the data to provide a best-fit line that closely corresponds to the data.

In one embodiment of the method and apparatus of the present invention, the data can be modified by use of a known filter, such as a low-pass filter or a high-pass

15   filter. Either digital or analog filters may be used. Either linear or nonlinear (e.g., median) filters may be used. By way of example, and not to limit the scope of the present invention, a low-pass filter may be applied to the measured VCO_2 signal. As another example, a high-pass filter may be applied to the measured $CaCO_2$ signal. Preferably, the filter and filter coefficient that are selected maximize the correlation

20   between the measured VCO_2 and $CaCO_2$ signals.

In another embodiment of the method and apparatus of the present invention, the data points can modified by clustering. That is, the data points that are grouped closest to other data points are assumed to most accurately represent the true VCO_2 and $CaCO_2$ of the patient. For example, the measured data with at least a predetermined

25   number of close, or similar (e.g., within a specified threshold), data points is retained, while measured data with less than the predetermined number of close data points is discarded. The retained data points are assumed to be located on or near the best-fit line. In clustering, only these closely grouped sets of data points are considered in recalculating the best-fit line for the data and, thus, the negative slope (i.e., $-1 \times m$) of

30   the best-fit line to determine the pulmonary capillary blood flow or cardiac output of the patient.

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Another embodiment of the method and apparatus of the present invention includes modifying the data points that are most likely to be closest to an accurately placed and oriented best-fit line. Each data point, which has a carbon dioxide elimination component (e.g., a y-ordinate component) and a component based on an indicator of carbon dioxide content (e.g., an x-ordinate component), is evaluated on the basis of a predetermined minimum expected pulmonary capillary blood flow and a predetermined maximum pulmonary capillary blood flow. Lines, or the equations therefor, for both minimum expected and maximum expected pulmonary capillary blood flows are located so as to intersect at each data point. Then, the number of the other data points that are located between the two pulmonary capillary blood flow lines or equations is determined for each data point. Only those data points with a threshold number of other data points between the two intersecting lines are used in the determination of the location and orientation of the best-fit line through the data.

Of course, any combination of methods of modifying data may be used to accurately determine the slope of the best-fit line through the measured VCO_2 and $PetCO_2$ data and, thus, to determine the pulmonary capillary blood flow or cardiac output of a patient.

The best-fit line through carbon dioxide elimination and carbon dioxide content data may also be used to determine the mixed venous carbon dioxide content of the patient when partial rebreathing techniques are employed to obtain the data. As the mixed venous carbon dioxide content is assumed to equal the carbon dioxide content of the patient's blood when carbon dioxide elimination ceases (which does not occur during partial rebreathing), a best-fit line obtained by use of partial rebreathing techniques can be used to noninvasively determine carbon dioxide content and, thus mixed venous carbon dioxide content, when carbon dioxide elimination is set at zero.

Other features and advantages of the present invention will become apparent to those of ordinary skill in the art through a consideration of the ensuing description, the accompanying drawings, and the appended claims.

BRIEF DESCRIPTION OF DRAWINGS

FIG. 1 is a schematic representation of an exemplary rebreathing circuit that may be employed with the methods of the present invention;

FIG. 2 is a schematic representation which illustrates the componentry that may be utilized to measure respiratory profile parameters that are employed in the methods of the present invention;

FIG. 3A illustrates an idealized, bi-directional rebreathing cycle with VCO_2 values for different breaths depicted as diamonds and $PetCO_2$ values for various breaths shown as squares;

FIG. 3B is a two-dimensional plot illustrating the use of a known, bi-directional rebreathing process to obtain three VCO_2 values and three values representative of the carbon dioxide content of the blood of a patient before, during, and after rebreathing; these three values have been used to substantially noninvasively determine the pulmonary capillary blood flow or cardiac output of the patient;

FIG. 3C is a two-dimensional plot of a number of VCO_2 values against the same number of carbon dioxide content values obtained over a single bi-directional rebreathing cycle;

FIG. 3D is an exemplary two-dimensional plot depicting VCO_2 and carbon dioxide content values from the same re-breathing cycle as that shown in FIG. 3C and modified in accordance with the method of present invention;

FIGs. 4A and 4B are two-dimensional plots illustrating an embodiment of a method for modifying data to obtain an accurate best-fit line therethrough in accordance with teachings of the present invention;

FIG. 5 is a two-dimensional line graph illustrating a typical plot of VCO_2 on they-axis and $CaCO_2$ on the x-axis; and

FIG. 6 is a two-dimensional line graph illustrating a plot of VCO_2 on the y-axis and $CaCO_2$ on the x-axis after the VCO_2 and $CaCO_2$ data have been modified in accordance with teachings of the present invention.

BEST MODES FOR CARRYING OUT THE INVENTION

The present invention includes use of the Fick equation to calculate pulmonary capillary blood flow or cardiac output as the ratio of a change in carbon dioxide elimination, or VCO_2, to a change in the content of carbon dioxide, or $CaCO_2$, in the arterial blood of a patient:

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$$Q = \frac{\Delta V_{CO_2}}{\Delta CaCO_2}.$$ (6)

$CaCO_2$, or the content of carbon dioxide in the arterial blood of a patient, can be noninvasively estimated by determining the $PetCO_2$, or partial pressure of carbon dioxide in the end tidal respiration of a patient and converting $PetCO_2$ to $CaCO_2$ by use of a standard carbon dioxide dissociation curve, as is known in the art, as follows:

$$\Delta CaCO_2 = s\Delta PetCO_2,$$ (7)

where s is the slope of the carbon dioxide dissociation curve and $\Delta PetCO_2$ is a change in the end tidal partial pressure of carbon dioxide of a patient effected by a change in ventilation. Thus, pulmonary capillary blood flow or cardiac output can also be calculated as follows:

$$Q = \Delta V_{CO_2}/s\Delta PetCO_2.$$ (8)

Other indicators of the carbon dioxide content in the blood of a patient, such as pCO_2, may be used in place of $PetCO_2$ or $CaCO_2$ to determine the pulmonary capillary blood flow or cardiac output of a patient.

V_{CO_2} and $PetCO_2$, $CaCO_2$, pCO_2, or other indicators of the carbon dioxide content in the blood of a patient can be calculated or determined on the basis of substantially noninvasively obtained respiratory flow and respiratory carbon dioxide pressure data.

FIG. 2 schematically illustrates an exemplary method of substantially noninvasively monitoring the respiration of a patient and of measuring the flow rates and carbon dioxide concentration of gas mixtures that are inhaled and exhaled by a patient 10 over the course of the patient's breathing, such as during normal respiration or during known rebreathing techniques. A flow sensor 12 of a known type, such as the differential-pressure type respiratory flow sensors manufactured by Novametrix Medical Systems Inc. ("Novametrix") of Wallingford, Connecticut (e.g., the Pediatric/Adult Flow Sensor (Catalog No. 6717) or the Neonatal Flow Sensor (Catalog No. 6718)), which may be operatively attached to a ventilation apparatus (not shown), as well as respiratory flow sensors based on other operating principles and manufactured or marketed by others, may be employed to measure the flow rates of the breathing of patient 10.

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A carbon dioxide sensor 14, such as the CAPNOSTAT® carbon dioxide sensor and a complementary airway adapter (e.g., the Pediatric/Adult Single Patient Use Airway Adapter (Catalog No. 6063), the Pediatric/Adult Reusable Airway Adapter (Catalog No. 7007), or the Neonatal/Pediatric Reusable Airway Adapter (Catalog No.

5   7053)), which are manufactured by Novametrix, as well as main stream and side stream carbon dioxide sensors manufactured or marketed by others, may be employed to measure the carbon dioxide concentration of gas mixtures that are inhaled and exhaled by patient 10.

Flow sensor 12 and carbon dioxide sensor 14 are connected to a flow monitor

10   16 and a carbon dioxide monitor 18, respectively, each of which may be operatively associated with a computer 20 so that data from the flow and carbon dioxide monitors 16 and 18 representative of the signals from each of flow sensor 12 and carbon dioxide sensor 14 may be detected by computer 20 and processed according to programming (e.g., by software) thereof. Preferably, raw flow and carbon dioxide signals from the

15   flow monitor and carbon dioxide sensor are filtered to remove any significant artifacts. As respiratory flow and carbon dioxide pressure measurements are made, the respiratory flow and carbon dioxide pressure data may be stored by computer 20.

Each breath, or breathing cycle, of patient 10 may be delineated as known in the art, such as by continuously monitoring the flow rate of the breathing of patient 10.

20   As use of the Fick equation to calculate pulmonary capillary blood flow or cardiac output requires that a change in VCO_2 and $CaCO_2$, $PetCO_2$, pCO_2 or another indicator of the carbon dioxide content in the blood of a patient be known, a change in effective ventilation is required. By way of example, and not to limit the scope of the present invention, rebreathing techniques, such as by use of a dead space 70 such as that

25   provided by the rebreathing circuit illustrated in FIG. 1, may be employed to cause a change in effective ventilation. FIG. 3A illustrates the changes that may occur when a bi-directional rebreathing process is used to effect a change in effective ventilation. The graph of FIG. 3A illustrates the typical changes in the VCO_2 (shown as diamonds) and carbon dioxide content measurements (e.g., $PetCO_2$, shown as squares) that may

30   occur between the baseline breathing (i.e., before rebreathing), during rebreathing, and the stabilization (i.e., after rebreathing) periods of an idealized (i.e., without noise) bi-directional rebreathing cycle. During rebreathing, VCO_2 changes from a baseline

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value (e.g., about 200 ml/min) to a during rebreathing plateau (e.g., of about 100 ml/min.) within about 3 or 4 breaths, whereas carbon dioxide content may take longer to change from a baseline value (e.g., 38 mmHg) to a plateau (e.g., about 35 mmHg).

5   FIG. 3B is a two-dimensional plot illustrates that one value, the plateau value, from each of the before, during, and after rebreathing phases of a bi-directional rebreathing process, such as that illustrated in FIG. 3A, were used to estimate pulmonary capillary blood flow or cardiac output. By way of contrast, in a method of determining pulmonary capillary blood flow or cardiac output incorporating teachings of the present invention, VCO_2 and carbon dioxide content data are continually

10   measured, providing a plot such as that shown in FIG. 3C, with data at 100 being based on before rebreathing measurements, data along arrow 102 being based on during rebreathing measurements, and data along arrow 104 being based on after rebreathing measurements. These data may be obtained by use of a single rebreathing cycle, over the course of a number of rebreathing cycles, at one or more discrete time intervals, or

15   on a breath by breath basis, where data is continually measured, calculated, and analyzed in accordance with the method of the invention so as to continually update or monitor the pulmonary capillary blood flow or cardiac output of a patient.

When rebreathing or other known techniques are used to cause a change in effective ventilation so as to facilitate the substantially noninvasive determination of

20   pulmonary capillary blood flow or cardiac output, respiratory flow and carbon dioxide pressure data are obtained during at least the before, during, and after stages of rebreathing. Total or partial rebreathing processes may be used in the method of the present invention. These respiratory flow and carbon dioxide pressure data are then used, as known in the art, to calculate VCO_2 and $PetCO_2$, as well as the changes in VCO_2

25   and $PetCO_2$ that occur with the change in effective ventilation.

The calculated VCO_2 and $PetCO_2$ data are then used to determine the pulmonary capillary blood flow or cardiac output of the patient, such as by use of the Fick equations presented above.

As an alternative, the pulmonary capillary blood flow or cardiac output of a

30   patient can be determined over the course of a plurality of breaths by expressing the calculated VCO_2 data and $CaCO_2$ data or data of another indicator of the content of carbon dioxide in the blood of a patient, such as $PetCO_2$ or pCO_2, in two-dimensions,

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such as on a two-dimensional (X-Y) line graph, with VCO_2 data points being measured on the y-axis and $PetCO_2$ data points being measured on the x-axis, then identifying a line that best fits the data, which is also referred to herein as a best-fit line.

For example, the equation for the best fit line is:

$$y = mx + b \tag{9}$$

or

$$m = \frac{y - b}{x}, \tag{10}$$

where y is the y-axis coordinate of a data point, x is the x-axis coordinate of the same data point, m is the slope of the line, and b is the offset value for the line. If VCO_2 is measured on the y-axis and $CaCO_2$ is measured on the x-axis, then

$$m = \frac{VCO_2 - b}{CaCO_2}. \tag{11}$$

The negative slope (i.e., $-1 \times m$) of the best-fit line through the VCO_2-$CaCO_2$ data would be equal to the pulmonary capillary blood flow or cardiac output of the patient:

$$-m = Q. \tag{12}$$

The best-fit line for the VCO_2 and $CaCO_2$ data is preferably determined by use of known linear regression techniques or any other known methodology for determining the relationship between two variables. The method of linear regression provides an accurate pulmonary capillary blood flow or cardiac output value based on a large number of VCO_2 and $CaCO_2$ data obtained over the course of one or more changes in effective ventilation. When linear regression is used, the slope (m) of the best-fit line for the data is calculated as follows:

$$m = Lxy/Lxx \tag{13}$$

and the offset (b) of the line is calculated by the following equation:

$$b = \Sigma y/n - m \times \Sigma x/n, \tag{14}$$

where

$$Lxx = \Sigma x^2 - (\Sigma x \times \Sigma x)/n, \tag{15}$$

$$Lyy = \Sigma y^2 - (\Sigma y \times \Sigma y)/n, \text{ and} \tag{16}$$

$$Lxy = \Sigma xy - (\Sigma x \times \Sigma y)/n, \tag{17}$$

and where n is the number of data points in the plot, Σx is the sum of all x-coordinate (i.e., $CaCO_2$ content) values, Σy is the sum of all y-coordinate (i.e., VCO_2) values, Σx^2 is the sum of the square of all x-coordinate values, Σy^2 is the sum of the square of all y-

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coordinate values, and Σxy is the sum all paired x- and y-coordinate values multiplied by each other.

When linear regression is used to determine the location and orientation of a best-fit line, a correlation coefficient (r) that quantifies the accuracy with which the best-fit line correlates to the VCO_2 and $CaCO_2$ data can also be calculated as follows:

$$r = (Lxy \times Lxy)/(Lyy \times Lxx). \tag{18}$$

Alternatively, any other measure of the quality of fit that quantifies the accuracy with which the best-fit line correlates to the VCO_2 and $CaCO_2$ data may be used.

Correlation coefficients range from 0 to 1.0, where a correlation coefficient of 0 indicates that no linear correlation exists between the x-ordinate and the y-ordinate data and a correlation coefficient of 1.0 indicates that the x-ordinate and y-ordinate data are perfectly linearly correlated (i.e., all of the VCO_2-$CaCO_2$ data points are located on the same straight line).

The VCO_2-$CaCO_2$ data points measured before and during rebreathing, however, are rarely located on the same straight line. One reason for this is that, during rebreathing maneuvers, the VCO_2 signal typically leads the $PetCO_2$ signal and, thus, the $CaCO_2$ by about one breath. In addition, VCO_2 is calculated on the basis of signal components that have higher frequencies than do the $PetCO_2$ signal. As a result, when the VCO_2 and $CaCO_2$ measurements calculated over a period of time are plotted against one another on a two-dimensional (X-Y) line graph, the result typically appears as an arc or a loop, as shown in FIGs. 3C and 5, rather than as a straight line, depending on the amount of data calculated and the duration of rebreathing. Moreover, VCO_2 and $CaCO_2$ measurements may be calculated on the basis of respiratory flow and carbon dioxide pressure data obtained during spurious breaths. Such data do not relate to the pulmonary capillary blood flow or cardiac output measurement. VCO_2 and $CaCO_2$ calculations that are based upon such spurious data act as noise that may result in miscalculation of a best-fit line through the calculated VCO_2 and $CaCO_2$ data. As a result, the correlation coefficient of a best-fit line to the data is typically much less than 1.0.

The measured respiratory flow and carbon dioxide pressure data or the calculated VCO_2 and $CaCO_2$ data can be modified to increase the correlation coefficient between the VCO_2 and $CaCO_2$ data and the best-fit line therefor. Preferably, a linear

transform is used to increase the correlation coefficient. A linear transform may be used to delay the calculation of a VCO_2 data point to accurately coincide therewith a $CaCO_2$ data point based on measurements taken during the same breath. The measured or calculated data may also be filtered by use of a linear transform.

5   In one embodiment of a method for increasing the correlation coefficient between the VCO_2 and $CaCO_2$ data and the best-fit line therefor, a filter is applied to the calculated VCO_2 or $CaCO_2$ data. Known analog or digital low-pass, high-pass, or band pass filters, including adaptive filters, may be employed. Linear or nonlinear may be employed. Preferably, a first order (single pole) infinite impulse response (IIR) digital

10   filter is employed to filter the VCO_2 calculations in a manner that improves the correlation between the VCO_2 calculation and the lagging $PetCO_2/CaCO_2$ calculation. The equation for such a filter is:

$$VCO_2`[n] = \alpha \times VCO_2`[n-1] + (1-\alpha) \times VCO_2[n], \tag{19}$$

where $VCO_2[n]$ is the most recently calculated, unfiltered VCO_2 data point, $VCO_2`[n-1]$ is

15   the previous, filtered VCO_2 data point, $VCO_2`[n]$ is the new "filtered" value based on $VCO_2[n]$ and obtained by use of the filter, and α is the filter coefficient. The filter coefficient, α, has a range of 0 to 1.0. The greater the value of α, the more profoundly the most recently calculated data point is filtered and, conversely, the lower α values cause the most recently calculated data points to be filtered to a lesser degree. When α

20   is equal to zero, the most recently calculated data point is not filtered.

Due to anatomical and physiological differences between different patients, different patients have differing optimal filter coefficients, α. In addition, as anatomical and physiological changes may occur in a patient over time, the optimum filter coefficients, α, to be used in filtering the VCO_2 or $CaCO_2$ values calculated from the

25   patient's breathing may also vary over time. Accordingly, the selection of an optimal filter coefficient, α, is also within the scope of the present invention. Any known optimization method or search algorithm may be employed to select optimal filter coefficient, α.

As an example of the way in which an optimal filter coefficient may be selected,

30   α is first set to a default value (e.g., 0.85) and the calculated VCO_2 or $CaCO_2$ values are filtered on the basis of the default filter coefficient, α. The linear regression is then performed to obtain a best-fit line. If the correlation coefficient of best-fit line

calculated with the just-filtered data is less than the correlation coefficient of the immediately preceding best-fit line, which was calculated with unfiltered data or with a prior filter coefficient, then a predetermined α adjustment value (e.g., 0.01) is changed by multiplying the α adjustment value by -1 and by modifying the filter coefficient by

5   adding the modified α adjustment value thereto. Otherwise, the filter coefficient, α, is modified by adding the unmodified α adjustment value thereto. The process of filtering the data based on a modified filter coefficient, obtaining a best-fit line for the data, comparing the correlation coefficient of the best-fit line to the correlation coefficient of the previous best-fit line, and adjusting the filter coefficient accordingly is then repeated

10   a predetermined number of times (e.g., 50 times). The best-fit line with the greatest correlation coefficient, based on the unfiltered data and each set of filtered data, is selected to calculate the pulmonary capillary blood flow or cardiac output of the patient. When filtering is used, the VCO_2-$CaCO_2$ plot preferably narrows, as depicted in FIGs. 3D and 6, to thereby increase the accuracy with which the location and

15   orientation of a best-fit line can be established and, thus, to increase the accuracy of a pulmonary capillary blood flow or cardiac output determination based on the data.

Another embodiment of a method for increasing the correlation coefficient between the VCO_2 and $CaCO_2$ data and the best-fit line therefor, which is referred to herein as "clustering," includes the selection of data points that are grouped closely

20   together. That is, the data points that are selected include those data points having a number of other data points within a predetermined range thereof. Data points that are not clustered are probably inaccurate or based on measurements taken during spurious breaths. As an accurate best-fit line through the data would likely be based on the clustered data, the data points that are not located in a cluster are not used in calculating

25   the location and orientation of a best fit line for the data.

Clustering of the data points may include normalization or transformation of the data such that ranges of the x-coordinate data (e.g., the $CaCO_2$ data) and the y-coordinate data (e.g., the VCO_2 data) are substantially the same. Without such normalization, the data group (e.g., the VCO_2 data or the $CaCO_2$ data) with the highest

30   range would dominate; the other data group would be less significant.

An exemplary manner in which the data may be normalized includes use of the following normalization:

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$$x = (x - \bar{x})/\sigma_x, \qquad (20)$$

where:

x is the raw value, $\bar{x}$ is the mean value of all x-axis (e.g., $CaCO_2$) data in the plot, and σ_x is the standard deviation of all x-axis data in the plot. This normalization is applied

5   to all x-axis values. A similar normalization scheme is applied to all of the y-axis values.

The normalized data may then be clustered by searching for a predetermined number (e.g., 5) of the closest data points (e.g., VCO_2 or $CaCO_2$ data points) to each of the data points in a group. The differences between the analyzed data point and each of

10   the predetermined number of closest data points are then added together and compared to a predetermined threshold. If the sum of the differences exceeds the predetermined threshold, the analyzed data point is discarded. Of course, the use of other clustering techniques to identify the most accurate data and to disregard probable inaccurate data are also within the scope of the present invention.

15   Once clustering has been performed, the inverse of the normalization is calculated, or the normalization is undone, to provide an accurate determination of pulmonary capillary blood flow or cardiac output. An example of the manner in which the inverse of the normalization may be calculated includes use of the following equation:

20    $$x = x\sigma_x + \bar{x}. \qquad (21)$$

This inverse of the normalization is applied to all of the clustered x-axis (e.g., $CaCO_2$) values. A similar inverse normalization scheme is applied to all of the clustered y-axis data.

Clustering is one of many known techniques for determining outliers. Other

25   known techniques for determining outliers may also be used in the method of the present invention.

Alternatively, or in addition to disregarding probable inaccurate data points, in order to enhance the accuracy of the data, clustering can be used add synthetic data points. Synthetic data points may be added to increase the correlation coefficient of the

30   best-fit line to the data points on which the best-fit line is based.

Another embodiment of the method for modifying data that incorporates teachings of the present invention is depicted in FIGs. 4A and 4B. As with the filtering

and clustering embodiments described previously herein, the present embodiment includes selection of data points that are most likely to facilitate an accurate determination of the location and orientation of a best-fit line and, thus, of the pulmonary capillary blood flow or cardiac output of a patient. This embodiment of the
5   method for modifying data includes iteratively examining data points and the distribution of the remaining data points relative to the two lines representing the range of possible PCBF measurements.

As shown in FIGs. 4A and 4B, a line or the equation for a line 110 representing a minimum expected pulmonary capillary blood flow (i.e., $-m_{line} = PCBF_{min}$) and a line
10   or the equation for a line 120 representing a maximum expected pulmonary capillary blood flow (i.e., $-m_{line\ 120} = PCBF_{max}$) are positioned to intersect at a data point 130. For example, when the x-ordinate is based on $CaCO_2$, line 110 may have a slope of -0.5, which represents a minimum expected pulmonary capillary blood flow of 0.5 L/min, and line 120 may have a slope of -20, which represents a maximum pulmonary
15   capillary blood flow of 20 L/min. Of course, the use of other pulmonary capillary blood flow values for lines 110 and 120 is also within the scope of the present invention.

Next, the number of other data points 130 located between lines 110 and 120 is determined. If the number of data points 130 between lines 110 and 120 is equal to or exceeds a threshold number, the analyzed data point 130 is retained for a subsequent
20   determination of the location and orientation of a best-fit line through the data. Otherwise, the analyzed data point 130 is discarded. The threshold number of data points that must be located between line 110 and line 120 for an analyzed data point to be retained may be a predetermined value or determined by other means. As example, the threshold number may be set to the median number of data points that are located
25   between line 110 and line 120 when each data point 130 of a set of data points 130 has been evaluated in accordance with the present embodiment of the method for modifying data. This process is repeated until each data point 130 in a set of data points 130 has been so evaluated. FIG. 4A depicts use of the present embodiment of the data modification method on a data point 130 that will be retained, while FIG. 4B illustrates
30   use of the present embodiment of the data modification method on another data point 130' that will not be retained.

FIGs. 3C and 3D and FIGs. 5 and 6 illustrate the effect of modifying data in accordance with teachings of the present invention to increase the accuracy with which the location and orientation of a best-fit line through the data may be determined. FIG. 5 illustrates a typical VCO_2 vs. $CaCO_2$ plot without such modification, where the

5   plot appears as a loop. By way of contrast, FIG. 6 illustrates the closeness of the data when one or more of the embodiments of the method of the present invention are used to modify the data. FIGs. 3C and 3D illustrate plots of VCO_2 and $PetCO_2$ data before and after modification in accordance with the present invention, respectively. The increased closeness of the data points makes it possible to determine the orientation and

10   location of a best-fit line therethrough with increased accuracy.

Once all of the data points have been examined, the location and orientation for the best-fit line through the remaining, clustered data are determined. Again, linear regression is preferably used to determine the location and orientation of the best-fit line. The negative slope (i.e., $-1 \times m$) of the best-fit line provides a pulmonary capillary

15   blood flow measurement, which may then be used to determine cardiac output. A correlation coefficient can then be calculated, as previously disclosed herein, to indicate the quality of the data used to determine pulmonary capillary blood flow or cardiac output. The correlation coefficient or a quality measure based thereon may then be communicated to the user (e.g., a doctor, nurse, or respiratory technician) or used to

20   weight the resulting pulmonary capillary blood flow or cardiac output value in an output weighted average value.

One or a combination of the embodiments of the method for modifying data in accordance with the present invention may be performed on the measured or calculated data to increase the accuracy with which a best-fit line through the data or the

25   pulmonary capillary blood flow or cardiac output of a patient can be determined.

As an example of the use of filtering and clustering together, the calculated VCO_2 data are grouped together as the y-axis data of a two-dimensional line graph and the calculated $CaCO_2$ data points are grouped together as x-axis data points. The data points in at least one of the groups are filtered to determine a best-fit line for the data

30   having an optimum correlation coefficient. The data are also clustered, either before or after filtering, to further improve the correlation coefficient of the best-fit line to the calculated VCO_2 and $CaCO_2$ data. The remaining data is then used to determine (e.g.,

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by linear regression) a best-fit line therefor, as well as a correlation coefficient for the best-fit line. The slope of the best fit line is then calculated and used to determine pulmonary capillary blood flow or cardiac output. The correlation coefficient may also be used to indicate the reliability of the pulmonary capillary blood flow or cardiac

5   output determination or to impart a specific weight to the pulmonary capillary blood flow or cardiac output determination in a weighted average thereof.

Once the location and orientation of an accurate best-fit line for the data has been determined, as disclosed previously herein, the pulmonary capillary blood flow of the patient can be calculated as the negative of the slope of the best fit line. In addition,

10   cardiac output can then also be determined by adding the pulmonary capillary blood flow of the patient to the intrapulmonary shunt flow of the patient, which can be determined by known processes.

In addition, the best-fit line can be used to estimate mixed venous carbon dioxide content of the patient. Conventionally, total rebreathing techniques have been

15   required to substantially noninvasively measure mixed venous carbon dioxide content. When carbon dioxide elimination eventually ceases during total rebreathing, the partial pressure of carbon dioxide measured at the mouth of a patient may represent the mixed venous carbon dioxide content of the patient. When partial rebreathing techniques are used, the carbon dioxide elimination of the patient is reduced to levels lower than

20   baseline, but is not reduced to zero. By employing teachings of the present invention to determine the best-fit line through data obtained by use of partial rebreathing techniques, the best-fit line can be extended to a point where carbon dioxide elimination would be equal to zero or effectively zero and thereby to determine the carbon dioxide content, or mixed venous carbon dioxide content, of the patient's blood

25   at that point. Equation (11), which is the equation for the best-fit line, can be rearranged in terms of carbon dioxide elimination as follows:

$$V_{CO_2} = m \times C_aCO_2 + b. \tag{22}$$

When carbon dioxide elimination ceases, V_{CO_2} is equal to zero and equation (22) becomes:

30     $$0 = m \times C_vCO_2 + b, \tag{23}$$

where C_vCO_2 is the mixed venous carbon dioxide content, which can be rearranged as follows:

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$$CvCO_2 = -b/m. \tag{24}$$

Accordingly, the present invention also includes a method for substantially noninvasively determining mixed venous carbon dioxide content when partial rebreathing techniques are employed.

5

Although the foregoing description contains many specifics, these should not be construed as limiting the scope of the present invention, but merely as providing illustrations of some of the presently preferred embodiments. Similarly, other embodiments of the invention may be devised which do not depart from the spirit or

10   scope of the present invention. Features from different embodiments may be employed in combination. The scope of the invention is, therefore, indicated and limited only by the appended claims and their legal equivalents, rather than by the foregoing description. All additions, deletions and modifications to the invention as disclosed herein which fall within the meaning and scope of the claims are to be embraced

15   thereby.

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CLAIMS

<u>What is claimed is:</u>

1.   A method for noninvasively determining at least one of a mixed venous carbon dioxide content, a pulmonary capillary blood flow, and a cardiac output of a patient, comprising:

determining a plurality of data comprising carbon dioxide elimination data and data of an indicator of carbon dioxide content in blood of the patient;

determining a correlation coefficient between said carbon dioxide elimination data and said data of said indicator of carbon dioxide content; and

calculating at least one of the mixed venous carbon dioxide content, the pulmonary capillary blood flow, and the cardiac output based on said correlation coefficient.

2.   The method of claim 1, wherein said determining said correlation coefficient comprises plotting said carbon dioxide elimination data against said data of said indicator of carbon dioxide content.

3.   The method of claim 2, wherein said plotting comprises plotting said carbon dioxide elimination data along a y-axis of a two-dimensional line graph against corresponding data of said indicator of carbon dioxide content plotted along an x-axis of said two-dimensional line graph.

4.   The method of claim 3, wherein said determining said correlation coefficient further comprises determining a best-fit line through the plotted plurality of data.

5.   The method of claim 4, wherein said calculating the pulmonary capillary blood flow includes multiplying a slope of said best-fit line by -1.

6.   The method of claim 1, further comprising modifying at least one of said carbon dioxide elimination data and said data of said indicator of carbon dioxide content to increase said correlation coefficient.

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7.   The method of claim 6, wherein said modifying comprises selecting data
to use in said determining said correlation coefficient, said selecting comprising at least
one of:

filtering at least one of said carbon dioxide elimination data and said data of said
5   indicator of carbon dioxide content;

clustering said carbon dioxide elimination data and said data of said indicator of carbon
dioxide content; and

determining a number of data points between a first line representing a minimum
expected mixed venous carbon dioxide content, pulmonary capillary blood flow,
10   or cardiac output and a second line intersecting said first line at an analyzed data
point of said plurality of data, said second line representing a maximum
expected mixed venous carbon dioxide content, pulmonary capillary blood flow,
or cardiac output and comparing said number to a threshold number in
determining whether to retain said analyzed data point.

15

8.   The method of claim 7, wherein said filtering is effected on the basis of
an infinite impulse response form employing the following equation:

$$V_{CO_2}`[n] = \alpha \times V_{CO_2}`[n-1] + (1-\alpha) \times V_{CO_2}[n],$$

where $V_{CO_2}[n]$ is the most recently obtained, unfiltered carbon dioxide elimination data
20 point, $V_{CO_2}`[n-1]$ is the previous, filtered carbon dioxide elimination data point,
$V_{CO_2}`[n]$ is the new "filtered" value based on $V_{CO_2}[n]$ and obtained by use of the filter,
and α is a filter coefficient.

9.   The method of claim 7, further comprising normalizing at least a portion
25 of said plurality of data prior to said clustering.

10.   The method of claim 9, further comprising reversing said normalizing
following said clustering and before said determining said correlation coefficient.

30   11.   The method of claim 1, wherein said determining said plurality of data
comprising data of an indicator of carbon dioxide content in blood of the patient
comprises determining $CaCO_2$ data or end tidal partial pressure data.

12.   A respiratory evaluation apparatus for noninvasively determining at least one of a mixed venous carbon dioxide content, a pulmonary capillary blood flow, and a cardiac output of a patient, comprising:

sensing means for obtaining a plurality of data comprising carbon dioxide elimination

5   data and data of an indicator of carbon dioxide content in blood of the patient;

first processing means for determining a correlation coefficient between said carbon dioxide elimination data and said data of said indicator of carbon dioxide content; and

second processing means for calculating at least one of the mixed venous carbon

10   dioxide content, the pulmonary capillary blood flow, and the cardiac output based on said correlation coefficient.

13.   The respiratory evaluation apparatus of claim 12, wherein said first processing means is configured to determine said correlation coefficient by plotting said

15   carbon dioxide elimination data against said data of said indicator of carbon dioxide content.

14.   The respiratory evaluation apparatus of claim 13, wherein said first processing means is configured to plot said carbon dioxide elimination data along a y-

20   axis of a two-dimensional line graph against corresponding $CaCO_2$ or end tidal partial pressure data plotted along an x-axis of said two-dimensional line graph.

15.   The respiratory evaluation apparatus of claim 14, wherein said first processing means is configured to determine said correlation coefficient by determining

25   a best-fit line through the plotted plurality of data.

16.   The respiratory evaluation apparatus of claim 15, wherein said second processing means is configured to effect said calculating the pulmonary capillary blood flow by multiplying a slope of said best-fit line by -1.

30

17.   The respiratory evaluation apparatus of claim 12, further comprising improvement means for modifying at least one of said carbon dioxide elimination data

and said data of said indicator of carbon dioxide content to increase said correlation coefficient.

18.   The respiratory evaluation apparatus of claim 17, wherein said

5   improvement means is configured to select data to use in determining said correlation coefficient and includes at least one of:

refinement means for filtering at least one of said carbon dioxide elimination data and said data of said indicator of carbon dioxide content;

grouping means for clustering said carbon dioxide elimination data and said data of said

10   indicator of carbon dioxide content; and

evaluation means for determining a number of data points between a first line representing a minimum expected mixed venous carbon dioxide content, pulmonary capillary blood flow, or cardiac output and a second line intersecting said first line at an analyzed data point of said plurality of data, said second line

15   representing a maximum expected mixed venous carbon dioxide content, pulmonary capillary blood flow, or cardiac output and comparing said number to a threshold number in determining whether to retain said analyzed data point.

19.   The respiratory evaluation apparatus of claim 18, wherein said

20   refinement means is configured to effect said filtering on the basis of an infinite impulse response form by employing the following equation:

$$V_{CO_2}`[n] = \alpha \times V_{CO_2}`[n-1] + (1-\alpha) \times V_{CO_2}[n],$$

where $V_{CO_2}[n]$ is the most recently obtained, unfiltered carbon dioxide elimination data point, $V_{CO_2}`[n-1]$ is the previous, filtered carbon dioxide elimination data point,

25   $V_{CO_2}`[n]$ is the new "filtered" value based on $V_{CO_2}[n]$ and obtained by use of the filter, and α is a filter coefficient.

20.   The respiratory evaluation apparatus of claim 18, wherein said grouping means is further configured to normalize at least a portion of said plurality of data prior

30   to said clustering.

21.   The respiratory evaluation apparatus of claim 20, wherein said grouping means is further configured to reverse said normalizing following said clustering and before said determining said correlation coefficient.

5   22.   The respiratory evaluation apparatus of claim 12, wherein said data of an indicator of carbon dioxide content in blood of the patient comprises $CaCO_2$ data or end tidal partial pressure data.

23.   The respiratory evaluation apparatus of claim 12, further including a 10   processor.
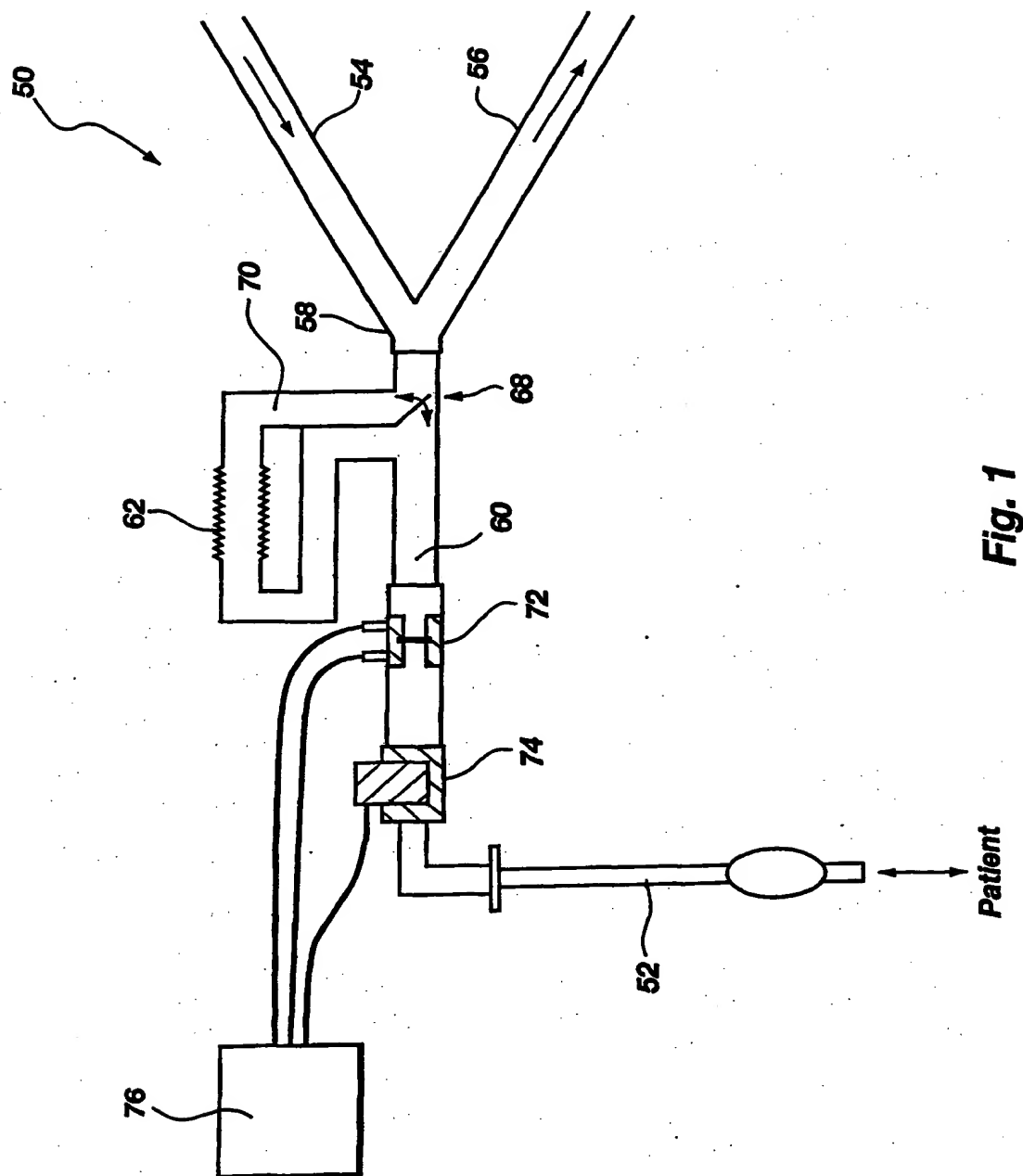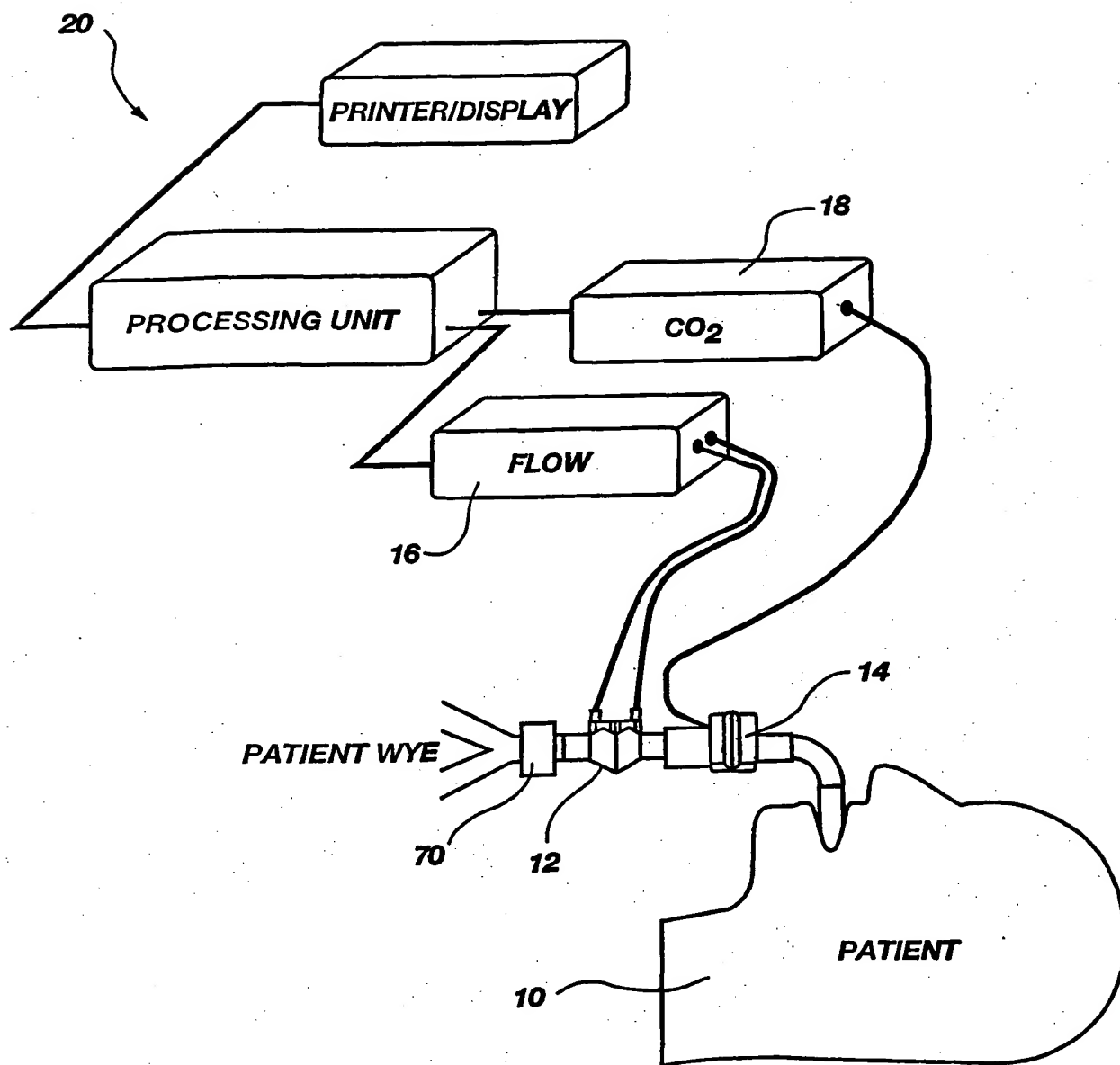
Fig. 1

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Fig. 2
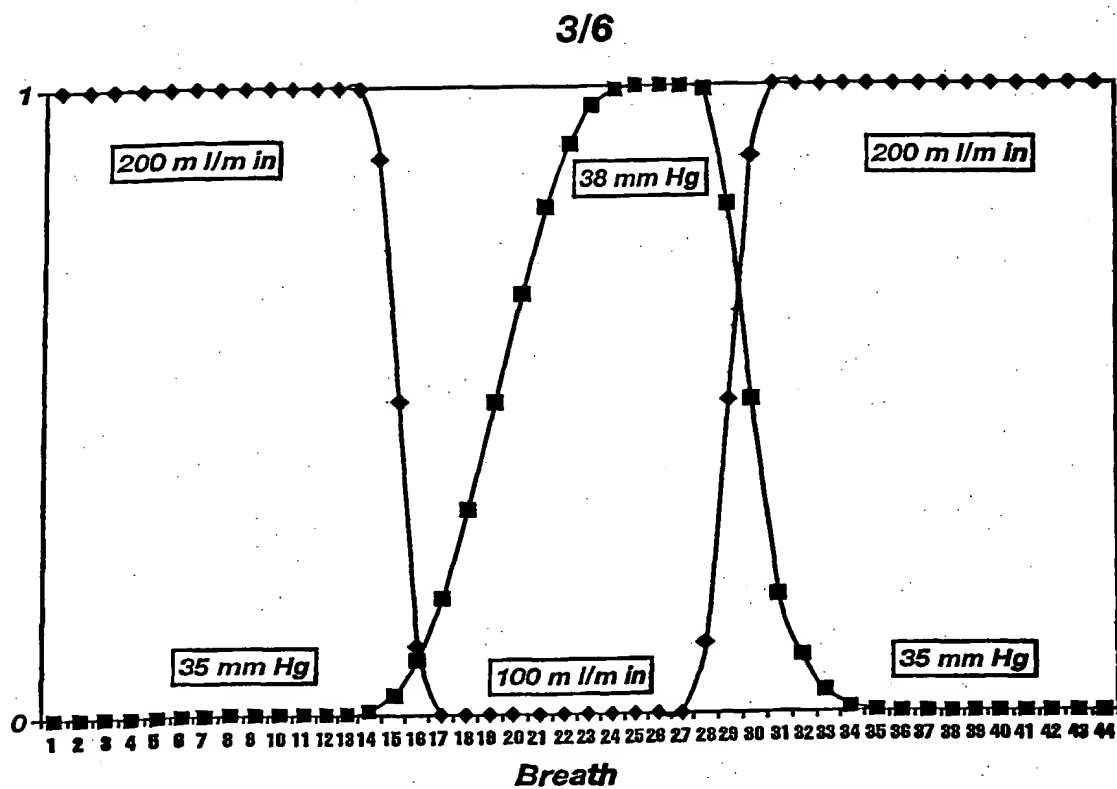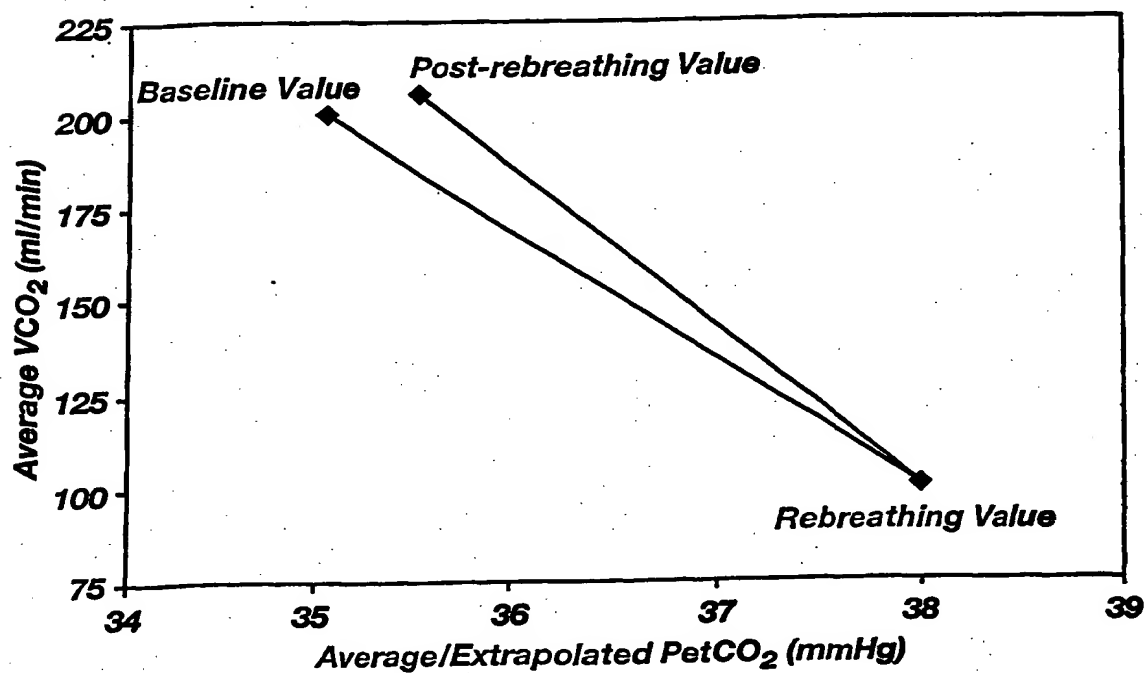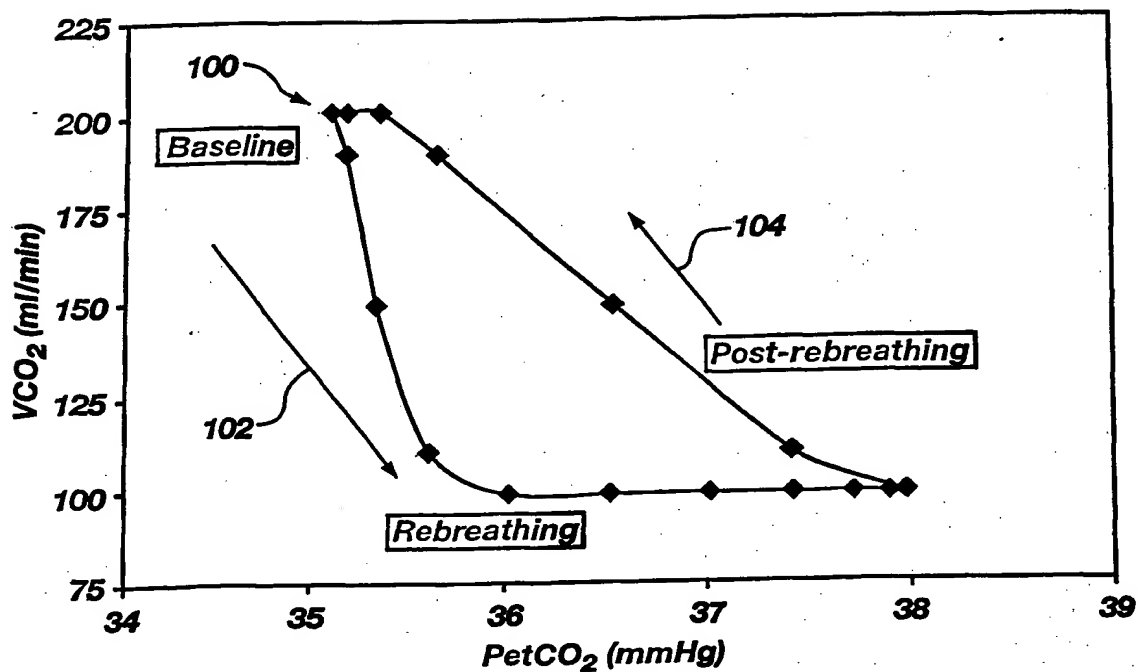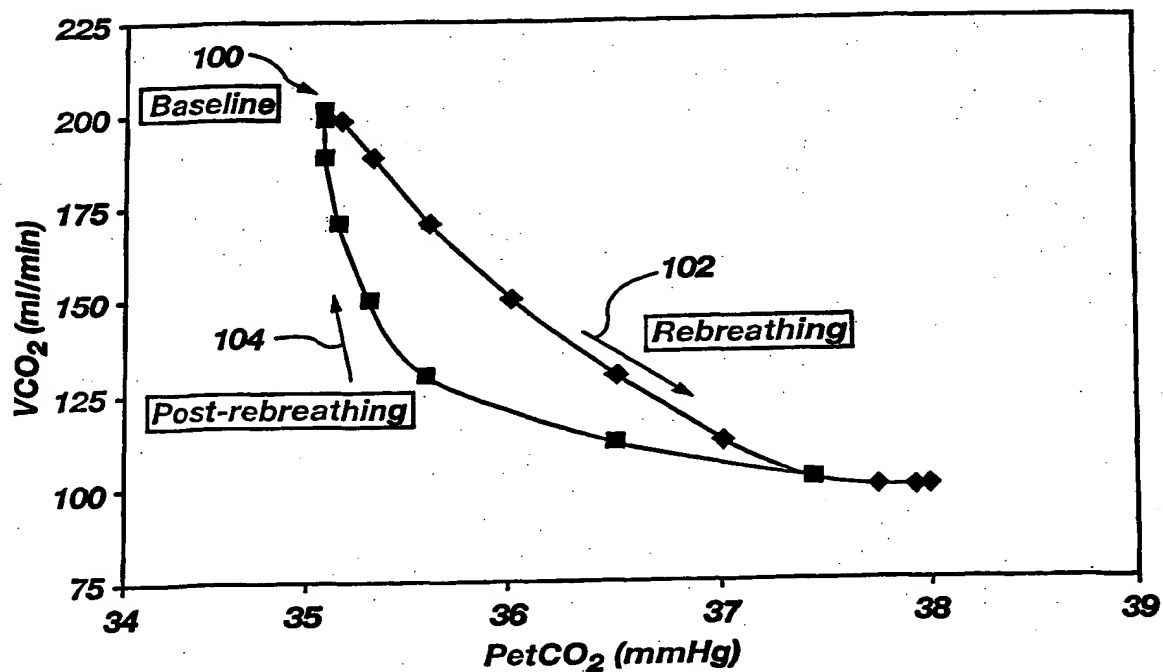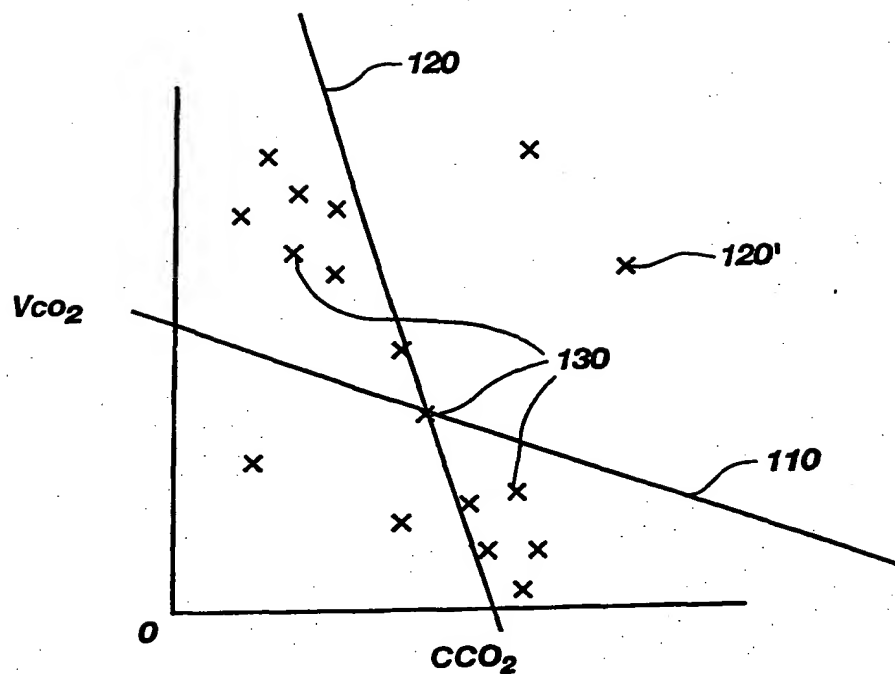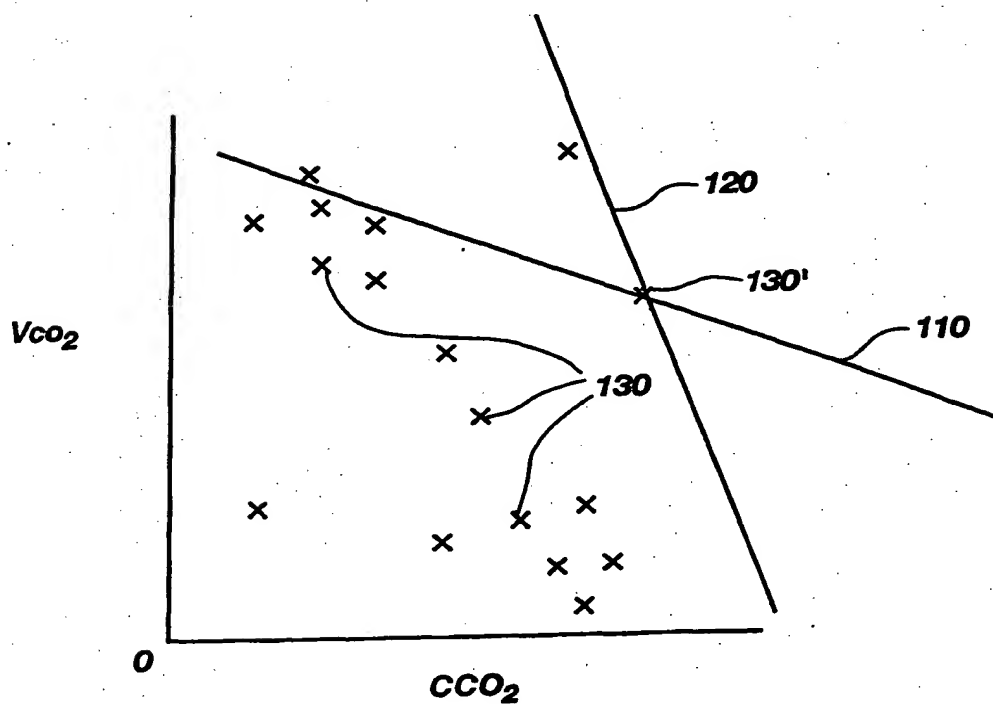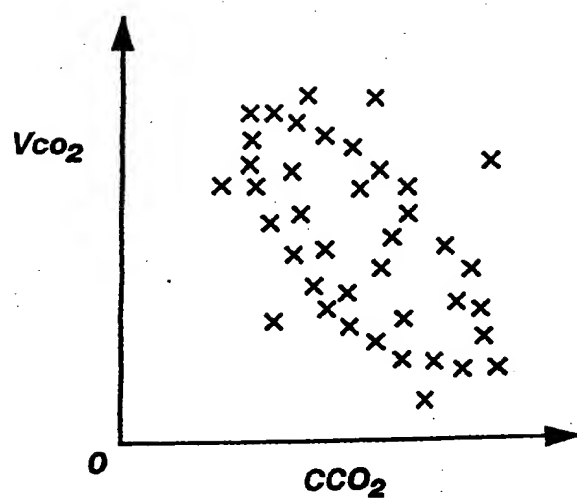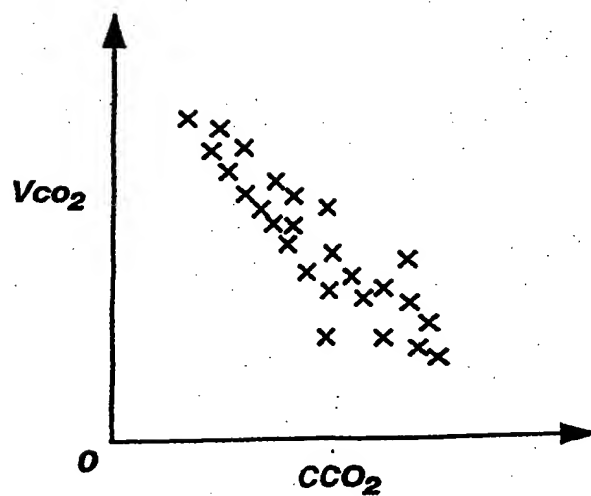
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Fig. 3A

Fig. 3B

Fig. 3C

Fig. 3D

Fig. 4A

Fig. 4B

Fig. 5

Fig. 6

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7   A61B5/083

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7   A61B   G06F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, INSPEC, COMPENDEX

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CAPEK J M ET AL.: "Noninvasive Measurement of Cardiac Output Using Partial CO2 Rebreathing" IEEE TRANSACTIONS ON BIOMEDICAL ENGINEERING, vol. 35, no. 9, September 1988 (1988-09), pages 653-661, XP002154963 New York, USA	1,6,7, 11,12, 17,18, 22,23
A	page 653, righ-hand column, line 12 - 22 page 655, left-hand column, line 5 - right-hand column, line 5	2,8,13, 19
X	DE 28 49 217 A (INSTITUT FÜR BIOMEDIZINISCHE TECHNIK) 29 May 1980 (1980-05-29) page 8, line 21 - page 11, line 5 page 4, line 1 - line 7	1,2,6,7, 12,13, 17,18,23

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[X] Further documents are listed in the continuation of box C.	[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
8 December 2000	27/12/2000

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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